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**Search:** L5

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**Search History**

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L2: Entry 46 of 46 File: DWPI Jul 31, 1991

DERWENT-ACC-NO: 1991-225137
DERWENT-WEEK: 200134


TITLE: Efficient ingestion of drugs from dry powder inhaler - using low rugosity particles crystallised from triple solvent mixt.

Basic Abstract Text (2):
ADVANTAGE - Redn. of the nigosity facilitates redispersion. Increased availability of the active agent also enables agents not hitherto suitable for oral inhalation to be admin. by this route. Examples of agents admin. are antihistamine and antiallergic cpds., beta-agonists, anti-cholimergics, sympathomimetic amimes, steroids (esp. corticosteroids), peptides, which cannot be conveniently admin. by other routes, and antibacterial agents. Other agents may also be employed, e.g. hypnotics, sedatives, tranquillisers, anti inflammatory agents, anti-tussives, anti-convulsants, muscle relaxants, anti-spasmodics, cardiovascular agents, antibiotics, and hypoglycaemic agents. A bronchodilator may be also present as additional active agent. The carrier is a crystalline sugar, selected from glucose, fructose, mannitol, sucrose, and lactose, esp. lactose. The ave. particle size is 30-250 microus, and the nigosity not more than 1.5. At least 80% by st. of the excipient comprises this carrier. The agent, comprising 0.1-50% by wt. of the compsn., is a particulate solid having ave. particle size 0.1-10 microus. It is a beta agonist, a steroid or sodium chromoglycoate, a peptide, esp. insulin or a growth hormone (ACTH and LNRH analogues, or an antibacterial agent, esp. pentamidine. The pptn. of the carrier material from son. is novel. The process involves pptn. of the carrier from a satd. aq. soln. by addn. of at least an equal vol. of a water immiscible solvent (WIS), and a solvent (MS) miscible with both water and WIS, comprising at least 5% by vol. of the aq. soln. The WIS is selected from hexane, CHCl3, cyclohexane, or toluene, and MS is selected from acetone, ErOH, PrOH, BuOH or MeCN.

Equivalent Abstract Text (1):
A particulate carrier suitable for use in dry powder inhaler compositions having an average particle size of from 5.0 to 1000 microns and a rugosity of less than 1.75.

Equivalent Abstract Text (2):
A particulate carrier suitable for use in dry powder inhaler compositions having an average particle size of from 5.0 to 1000 microns and a rugosity of less than 1.75.

Equivalent Abstract Text (6):
The carrier is a saccharide selected from the group consisting of a monosaccharide, a disaccharide and a polysaccharide and having an average particle size of from 5.0 to 1000 microns and a rugosity as measured by air permeametry of less than 1.75.

Equivalent Abstract Text (7):
It is selected from the group consisting of a monosaccharide and a disaccharide and a monosaccharide selected from the group consisting of glucose, fructose and mannitol. The particles have an average particle size of from 30 to 250 microns and a rugosity of not more than 1.5.

L5: Entry 74 of 75 File: USPT Apr 22, 1980

US-PAT-NO: 4199578
DOCUMENT-IDENTIFIER: US 4199578 A
**** See image for Certificate of Correction ****

TITLE: Composition

DATE-ISSUED: April 22, 1980

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Stevenson; Neil A. | Loughborough | | | GB2 |

US-CL-CURRENT: 514/171; 514/180

CLAIMS:

I claim:

1. A pharmaceutical composition for inhalation therapy, comprising a mixture of particulate beclomethasone dipropionate, at least 90% by weight of the particles of beclomethasone dipropionate having an effective particle size below 10 micrometers, and a powder carrier of effective particle size for administration of said composition by inhalation.

2. A composition according to claim 1, which comprises a mixture of beclomethasone dipropionate, at least 90% by weight of the particles of which have an effective particle size below 10 micrometers, and a carrier acceptable in the nose or lung, at least 90% by weight of the particles of the carrier having an effective particle size below 400 micrometers, and at least 50% by weight of the particles of the carrier having an effective particle size above 30 micrometers.

3. A composition according to claim 2, wherein at least 90% by weight of the particles of beclomethasone dipropionate have an effective particle size in the range 1 to 10 micrometers and at least 50% by weight of the particles of beclomethasone dipropionate have an effective particle size in the range 2 to 6 micrometers.

4. A composition according to claim 2, wherein at least 95% by weight of the particles of carrier have an effective particle size below 400 micrometers.

5. A composition according to claim 4, wherein at least 50% by weight of the carrier particles have an effective particle size in the range 30 to 150 micrometers.

6. A composition according to claim 5, wherein at least 50% by weight of the carrier particles have an effective particle size in the range 30 to 80 micrometers.

7. A composition according to claim 1, comprising from 0.01 to 2% by weight of beclomethasone dipropionate.

8. A composition according to claim 7, comprising from 0.01 to 1% by weight of

beclomethasone dipropionate.

9. A composition according to claim 8, comprising from 0.02 to 0.5% by weight of beclomethasone dipropionate.

10. A composition according to claim 1, wherein the carrier is lactose.

11. A composition according to claim 1 comprising a bronchodilator.

12. A composition according to claim 11, wherein the bronchodilator is orciprenaline, terbutaline or salbutamol or a pharmaceutically acceptable salt of any one thereof.

13. A composition according to claim 1 in a sealed capsule.

14. A capsule containing from 10 to 50 mg of a composition according to claim 1.

15. A capsule loosely filled to less than 80% by volume with a composition according to claim 1.

16. A composition according to claim 1 packed in an opaque container.

17. A capsule containing beclomethasone dipropionate in unit dosage form.

18. A pharmaceutical composition for inhalation therapy, comprising a mixture of beclomethasone dipropionate and a bronchodilator.

19. A method of treatment of asthma or hay fever which comprises inhalation administration of a composition according to claim 1 to a patient suffering from asthma or hay fever.

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L4: Entry 88 of 93 File: USPT Mar 18, 1997

US-PAT-NO: 5612053
DOCUMENT-IDENTIFIER: US 5612053 A

TITLE: Controlled release insufflation carrier for medicaments

DATE-ISSUED: March 18, 1997

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Baichwal; Anand | Wappingers Falls | NY | | |
| Staniforth; John N. | Bath | | | GB2 |

US-CL-CURRENT: 424/440; 424/434, 424/488, 424/499, 424/500

CLAIMS:

What is claimed is:

1. A respirable particle-based pharmaceutical formulation for delivering a medicament via insufflation, comprising controlled release particles of a cohesive composite of a medicament and a pharmaceutically-acceptable carrier comprising a polysaccharide gum of natural origin, wherein the average particle size of the said cohesive composite particles is from about 0.1 to about 125 microns in diameter.

2. The formulation of claim 1, wherein the average particle size of said cohesive composite particle is from about 0.1 to about 10 microns.

3. The formulation of claim 1, wherein the average particle size of said cohesive composite particle is from about 10 to about 125 microns.

4. The formulation of claim 1, wherein said polysaccharide gum comprises a heteropolysaccharide gum.

5. The formulation of claim 1, wherein said polysaccharide gum comprises a homopolysaccharide gum.

6. The formulation of claim 1, wherein said polysaccharide gum comprises a starch.

7. The formulation of claim 4, wherein said heteropolysaccharide gum is xanthan gum.

8. The formulation of claim 4, wherein said heteropolysaccharide gum is locust bean gum.

9. The formulation of claim 1, wherein said polysaccharide gum comprises a heteropolysaccharide gum and a homopolysaccharide gum in a ratio of from about 1:3 to about 3:1.

10. The formulation of claim 1, wherein the medicament polysaccharide to gum ratio is from about 0.5:100 to about 1:1.

11. The formulation of claim 10, wherein the medicament polysaccharide to gum ratio is from about 1:100 to about 1:2.

12. The formulation of claim 1, further comprising from about 0.1 to about 50% by weight of a cationic cross-linking agent comprising an alkaline metal or an alkaline earth metal sulfate, chloride, borate, bromide, citrate, acetate or lactate.

13. The formulation of claim 12, wherein said cationic cross-linking agent is present in an amount of from about 1 to about 10% by weight.

14. The formulation of claim 12, wherein said cationic cross-linking agent is selected from the group consisting of potassium chloride and sodium chloride.

15. The formulation of claim 1, wherein said pharmaceutically acceptable carrier further comprises an inert saccharide diluent selected from the group consisting of monosaccharides, disaccharides and mixtures thereof.

16. The formulation of claim 15, wherein said inert saccharide diluent is selected from the group consisting of dextrose, sucrose, galactose, lactose and mixtures thereof.

17. The formulation of claim 1, wherein said pharmaceutically acceptable carrier further comprises a pharmaceutically-acceptable surfactant in an amount of from about 0.5 to about 3% by weight of the controlled release carrier.

18. The formulation of claim 17, wherein said surfactant is selected from the group consisting of pharmaceutically-acceptable anionic surfactants, cationic surfactants, amphoteric (amphipathic/amphophilic) surfactants, non-ionic surfactants, and mixtures thereof.

19. The formulation of claim 1, wherein said controlled release particles are compressed together to form a solid mass.

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L5: Entry 73 of 75 File: USPT Mar 18, 1997

DOCUMENT-IDENTIFIER: US 5612053 A
TITLE: Controlled release insufflation carrier for medicaments

Brief Summary Text (7):
Another group of products are known as inhalations or insufflations. The British Pharmacopoeia defines an inhalation as a liquid drug delivery system whereas an insufflation is a powder delivery system for the respiratory tract. One such inhalation device is the pressurized metered dose inhaler (PMDI). Devices of this type are intended for delivering metered doses of a drug to the respiratory tract and include suspensions or solutions in a liquefied gas propellent, along with materials such as co-solvents (e.g., alcohol) and surfactants (e.g. lecithin). A metered dose inhaler contains multiple doses, often in the range of one to two hundred doses. The dose delivered is generally in the range of 25 to 100 microliters (.mu.l) per actuation.

Brief Summary Text (9):
Increasing attention is now being given in the art to dry powder inhalers.

Brief Summary Text (10):
For example, International Patent Application WO 94/04133 describes a powder composition for inhalation which contains a microfine drug such as a salbutamol sulfate and a carrier containing an anti-static agent. The carrier is calcium carbonate or a sugar, especially lactose. The amount of carrier is 95-99.99 weight percent. The compositions were said to be useful for delivery of the active agent to the lungs while providing reduced side effects such as nausea by maximizing its proportion of drug reaching the lungs.

Brief Summary Text (13):
Previously, a hetero-disperse polysaccharide excipient system and controlled release oral solid dosage forms were described in our U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757, all of which are hereby incorporated by reference. These systems are commercially available under the tradename TIMERx.TM. from TIMERx Technologies, Patterson, N.Y. and Edward Mendell Co., Inc., N.Y., which is the assignee of the present invention.

Brief Summary Text (46):
In certain formulations of the invention, it may be desirable to add a pharmaceutically acceptable surfactant in a sufficient amount to either modify the release-controlling characteristics of the composite excipient/drug particles or the wetting and solubility characteristics of the drug. In such embodiments, the surfactant comprises from about 0.01 to about 10 percent of the controlled release carrier, by weight, and more preferably from about 0.1 to about 2 percent of the controlled release carrier, by weight. The surfactants which may be used in the present invention generally include pharmaceutically acceptable anionic surfactants, cationic surfactants, amphoteric (amphipathic/amphiphilic) surfactants, and non-ionic surfactants. Suitable pharmaceutically acceptable anionic surfactants include, for example, monovalent alkyl carboxylates, acyl lactylates, alkyl ether carboxylates, N-acyl sarcosinates, polyvalent alkyl carbonates, N-acyl glutamates, fatty acid-polypeptide condensates, sulfuric acid esters, and alkyl sulfates.

Brief Summary Text (50):
The inert filler of the sustained release excipient preferably comprises a

pharmaceutically acceptable saccharide, including a monosaccharide and/or a disaccharide. Examples of suitable inert pharmaceutical fillers include sugars such as sucrose, dextrose, lactose, galactose, fructose, mixtures thereof and the like as well as sugar alcohols such as mannitol, sorbitol, xylitol, lactitol, maltitol, galactitol and the like. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, galactose, sucrose, or mixtures thereof be used. In addition, it is to be understood that the above-mentioned sugars and sugar alcohols can also be used as carriers as well, in place of or in addition to the materials described above.

Brief Summary Text (51):
The properties and characteristics of a specific controlled release carrier or excipient system prepared according to the present invention is dependent in part on the individual characteristics of the homo- and heteropolysaccharide constituents, in terms of polymer solubility, glass transition temperatures etc. In certain embodiments which include both a hetero- and homopolysaccharide component with or without optional polysaccharide filler (e.g., lactose), the properties and characteristics of the resultant dry powder formulation will also be dependent in part on the synergism both between different homo- and heteropolysaccharides and between the homo- and heteropolysaccharides (severally or together) and the inert saccharide constituent(s) in modifying dissolution fluid -excipient interactions.

Brief Summary Text (56):
The contacted drug-polysaccharide wet mass can then be granulated in the usual way using either a high speed mixture granulator or spray granulated to provide liquid contact or other suitable method to provide composite particles in the entrainable size range (for delivery from an insufflator) usually 45-355 microns (and preferably 63-95 microns for non-compression insufflation). The powder or granular material is then dried, for example, using a tray drier or fluidized bed drier operated at approximately 60.degree. C. for a sufficient time to produce equilibrium moisture content conditions in the powder/granules. In the case of some drugs/bioactives using a freeze drying method so as to avoid physical/chemical degradation. Finally, for some presentations ( inhaler types or clinical uses), it may be desirable to apply a final further size reduction to the dried powder/granules. This can be carried out using one of the methods described above or by sieving.

Brief Summary Text (76):
In general, insufflation inhalation devices suitable for use in connection with the inventive controlled release particulate dosage forms comprise a housing having a passageway for the flow of air, in which one end of the passageway is designed for insertion in the mouth or nose, a chamber containing controlled release particles of a cohesive composite of a medicament together with a pharmaceutically acceptable polysaccharide carrier suitable for oral inhalation, wherein the average discrete particle size is from about 0.1 to about 10 microns in diameter for the or-pulmonary route or 10 to 355 microns for the nasal route, actuating means for releasing a unit dose of the particles into said passageway, such that the unit dose is drawn through said passageway during an inspiration by the patient and is delivered to the naso-pharynx and/or the pulmonary tract of the patient.

Brief Summary Text (82):
Another device for delivery of inhalation powders is described in U.S. Pat. No. 2,587,215 (Priestly), hereby incorporated by reference. Priestly describes an inhaler having a storage chamber containing a powdered medicament, a mixing chamber and means to move a set dose of medicament from the storage chamber to the mixing chamber. The dose is mixed with air in the mixing chamber and inhaled through a mouthpiece.

Brief Summary Text (83):
Yet another inhalation device suitable for delivering powdered inhalation drugs is described in U.S. Pat. No. 4,274,403 (Struve), hereby incorporated by reference. Struve describes an inhaler for administering a powdered drug nasally, which includes storage means for containing a quantity of the drug therein. The storage means includes a feed hole through which the powdered drug may be received from the storage means. The device further includes a dispensing head operatively coupled to the storage means for dispensing the powdered drug more nasally. The dispensing head

of the Struve inhaler includes a nozzle, a body portion, a dispensing cylinder and a vent means. The nozzle is shaped to be received in the nasal passage of the user. The nozzle includes a dispensing passageway for dispensing the dose into the nasal cavity of patient.

Brief Summary Text (85):
The dispensing cylinder includes a metering chamber. The metering chamber may be selectively aligned with either the feed hole or the dispensing passageway. The dispensing cylinder is slidably received in the transverse bore for movement between a first transverse position in which the metering chamber is aligned with the feed hole and a second transverse position in which the metering chamber is aligned with the dispensing passageway. In its first position, the metering chamber can be filled with a charge of the powdered drug when the inhaler is manipulated. In the second position, places the charge of the powdered drug into the dispensing passageway for inhalation by the user.

Brief Summary Text (87):
Another inhaler device is disclosed in U.S. Pat. No. 4,524,769 (Wetterlin), hereby incorporated by reference. Wetterlin describes a dosage inhaler for administering a micronized pharmacologically active substance to a patient. The inhaler includes a gas conduit means through which gas passes for carrying the micronized substance to be administered. The inhaler further includes a membrane having a plurality of preselected perforated portions, each portion adapted to hold and dispense a reproducible unit dose of less than 50 mg of said active substance, in dry powder form. The powder particles have a particle size of less than 5 micrometers. The membrane is movably connected to the gas conduit means so that one of the preselected portions can be positioned within the gas conduit means so that the substance held in the preselected portion may be dispensed. The remaining preselected portion can be in a position external to said gas conduit means to receive said active substance. The membrane is movable through a plurality of positions whereby each preselected portion of the membrane can be successively positioned within the gas conduit to dispense the unit dose of the active substance held therein. Each preselected portion from which the active substance has been dispensed can be moved to said external position to receive active substance.

Brief Summary Text (88):
GB Patent Application No. 2,041,763, hereby incorporated by reference, describes an inhaler having a powder storage chamber and a rotatable metering member having dosing holes which open to the storage chamber in one position and open to the mixing chamber in another position. Upon rotation of the metering member, the powder is carried from the storage chamber to the mixing chamber to be inhaled.

Brief Summary Text (89):
EP 0 079 478, hereby incorporated by reference, describes an inhaler having a storage chamber, inhalation air passage and rotatable delivery member having a cavity formed therein. The delivery member is rotated from one position in which the cavity receives powder from the storage chamber to another position in which the powder falls from the cavity by the effect of gravity into a collector positioned in the air passage.

Brief Summary Text (90):
U.S. Pat. No. 4,860,740 (Kirk et al.), hereby incorporated by reference, describes an inhaler having a rotatable metering member with recesses formed therein. The recesses contain a powdered medicament. Upon rotation of the metering member, one of the recesses in exposed to the air inhalation passage to be entrained in the air stream and inhaled.

Brief Summary Text (98):
The cohesive composite particles comprising the dry powder insufflation formulations of the invention are capable of being compressed into a solid mass for insertion into a suitable inhalation device. In the event that the formulation is to be compressed, an effective amount of any generally accepted pharmaceutical lubricant, such as HVO or PEG, may be added to the above-mentioned ingredients of the excipient at the time the medicament is added, or any time prior to compression into a solid dosage form. Suitable lubricants can be added in an amount of from about 0.5% to

about 3% by weight of the solid dosage form. An especially preferred lubricant is sodium stearyl fumarate, NF, commercially available under the trade name Pruv.RTM.from the Edward Mendell Co., Inc.

Detailed Description Text (13):
In this example, 40.0024 grams of lactose and 5.0217 grams of a solution containing 16.0165 grams of albuterol sulfate in 200.05 grams of ethanol are added to a food processor and blended for 1 minute. The resultant wet granulate is screened through a 355 micron sieve. The screened composite is then dried at 60.degree. C. to about 4 percent LOD. The dried composite is then screened through 45, 63, and 125 micron sieves. The less than 45 micron, 45-63 micron, and 63-125 micron fractions are separately packed in sealed bottles containing a desiccant cartridge.

Detailed Description Text (16):
In this example, the products of Examples 1-3 were studied to determine drug delivery of the respective formulations. The fraction containing 45-63 micron particles for each of the products prepared in Examples 1-3 were placed into size 3 gelatin capsules (20 mg .+-.2 mg). The 45-63 micron fraction was selected to insure shallow lung penetration. The studies were conducted using a Twin Stage Impinger (TSI) apparatus A as described in British Pharmacopeia, 1993, Vol. II (Appendix XVII C, page A 194), incorporated by reference herein. The TSI and monograph provide a determination of the deposition of a dose emitted from a pressurized inhaler. According to the monograph, the upper and lower impingement chambers correspond to shallow lung and deep lung regions. Thus, by measuring the amount of active ingredient recovered from each chamber, the artisan can determine the amount of drug delivered to each area which is measured as a percentage of the total dose.

Detailed Description Text (19):
From the foregoing data, it can be seen that the products of examples 1 and 2 where the drug is associated with a polysaccharide, the amount of drug released at time =0 into both chambers is zero or close to zero and increases over the release periods studied in a controlled manner. In the case of the product of example 3, in which the drug is only associated with lactose, the total payload of drug available for release is released at time=0 with no significant further drug release after that time period. Therefore, the drug concentration, drug:polysaccharide ratio, and manner of drug loading on the carrier are significant controlling or influencing drug release from the insufflation formulations of the present invention.

CLAIMS:

16. The formulation of claim 15, wherein said inert saccharide diluent is selected from the group consisting of dextrose, sucrose, galactose, lactose and mixtures thereof.

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L2: Entry 40 of 46 File: USPT Dec 27, 1994

DOCUMENT-IDENTIFIER: US 5376386 A
TITLE: Aerosol carriers

Abstract Text (1):
Pharmaceutical excipients useful in dry powder inhalents comprise particles having a rugosity (measured by air permeametry) of less than 1.75. The use of these carriers increases the amount of drug injested by the patient using a dry powder inhaler. The preferred excipients are crystalline sugars such as lactose which may conveniently be prepared by controlled crystallisation from an aqueous medium.

Brief Summary Text (4):
The present invention is directed to novel materials which are useful as carriers in dry powder inhaler compositions. We have discovered that the redispersion of drug particles from compositions comprising carriers is facilitated if the rugosity of the carrier particles is reduced. The rugosity values of the materials are those measured by air permeametry. Accordingly, from one aspect our invention provides a particulate carrier suitable for use in the preparation of pharmaceutical compositions having an average particle size of from 5.0 to 1000 microns and a rugosity of less than 1.75. The measurement of rugosity by air permeametry produces a result which reflects the nature of the external surface of the material under test whereas measurements by techniques such as nitrogen adsorption reflect the total surface area including areas which are not accessible to particulate solids. The rugosity of conventional excipients measured by air permeametry has been found to be at least 1.96 and generally greater than 2.0. The carrier may be any crystalline non toxic material which is acceptable for use in pharmaceutical compositions which does not destabilise the pharmaceutically active materials with which it is formulated and which can be produced in a form having a rugosity of less than 1.75. The use of carriers which are significantly hygroscopic is less preferred. Such materials inevitably pick up moisutre during encapsulation and this reduces the ease with which the drug particles can be dispersed. Preferably the carrier will be as dry as possible prior to encapsulation. The preferred carriers are those which are known to be useful in dry powder inhaler compositions especially the mono-saccharides such as fructose, mannitol, arabinose, xylitol and dextrose (glucose) and their monohydrates, dissacharides such as lactose maltose or sucrose and polysaccharides such as starches, dextrins or dextrans.

Brief Summary Text (5):
Preferably the carrier comprises a particulate crystalline sugar or sugar alcohol which has a low affinity for water for example dextrose, fructose, sucrose or most preferably lactose.

Brief Summary Text (7):
The particulate sugar crystals which constitute a preferred aspect, may be conveniently prepared by crystallisation from a solution which is preferably an aqueous solution. The conditions under which crystallisation occurs should be controlled so as to favour the production of crystals having the desired low degree of rugosity. In general conditions which allow the crystals to form slowly are preferred whilst those which result in rapid crystallisation are correspondingly less preferred. The utility of any particular crystallisation process must be evaluated empirically and it is within the skill of the art to modify unsatisfactory procedures in order to produce the desired crystalline form of the novel excipients.

Brief Summary Text (10):
The size and morphology of the particulate material may be varied by controlling the conditions under which crystallisation and crystal growth occurs. In particular, the choice of the organic water immiscible solvent and the miscible solvent may exert a considerable influence. Examples of water immiscible solvents which may usefully be employed include hexane, chloroform cyclohexane, and toluene. Examples of miscible solvents include acetone, alcohols and acetonitrile. The requirement that the miscible solvent is at least partially miscible with the water immiscible solvent (and with water) means that the choice of immiscible and miscible solvents are interdependent. In the case of crystallisation of solutions of lactose, the preferred solvents are hexane (the immiscible solvent) and acetone (the miscible solvent). The quantities of solvent employed are preferably such as to provide an excess volume of immiscible solvent (typically at least 1.25 and more usually at least 1.5 times the volume of the saturated lactose solution being employed) and a relatively small quantity of the miscible solvent, say no more than 20% by volume being employed.

Brief Summary Text (12):
The form and size of the crystals may be determined by optical and/or scanning electron miscroscopy. The rugosity of the particles may be determined by air permeametry which relates the volumetric flow rate (Q) of air through a packed bed of powder compressed to a known porosity to the internal surface area So of the powder. The rugosity can then be expressed as the ratio So/Sd where Sd is theoretical surface area (assuming the particles to be spherical). In practice the smoothness of the particles may be readily apparent under the scanning electron microscope and this may render the determination of their rugosity superfluous. Preferably the particles will have a rugosity of no more than 1.5 and most preferably no more than 1.3.

Detailed Description Text (4):
Lactose (lactochem Pharmaceuticals), in a size range of 63-90 .mu.m was obtained by sieving (Alpine air jet sieve).

Detailed Description Text (5):
Recrystallised lactose was obtained by crystallisation of the original lactose in a partially miscible mixture of water, hexane and acetone.

Detailed Description Text (6):
Lactose was dissolved in water (2 to 1) in a beaker at 80C. The solution was cooled to room temperature, 75 ml of hexane (Reagent grade) was added to 50 ml of the saturated solution and agitated at 500 rpm with a paddle type agitator with four blades, acetone (10 ml) (Reagent grade) was then added. The mixture was stirred for 8-12 h, during which time lactose crystals formed. These were washed with acetone, absolute ethanol, 60% ethanol in water and absolute ethanol respectively and dried.

Detailed Description Text (7):
The particle size of the recrystallised lactose was determined with the optical microscope and was found to be in the range of 60-90 .mu.m. The examination of the carrier surface was by scanning electron microscopy. The rugosity of the lactose before and after crystallisation was determined by compressing a mass of powder equal to its density to a known porosity in the cell of a Fisher Sub-Sieve Sizer. The flow rate through the bed at a fixed pressure differential is transcribed by the instrument to an average particle diameter dm. The specific surface So was calculated from the equation ##EQU1## where p is the powder density. The rugosity before crystallisation was found to be 2.36 whilst the rugosity after recrystallisation was found to be 1.16.

Detailed Description Text (8):
Samples of drug -lactose blends were prepared in a ratio of 1:67.5 by mixing the micronised drug and the treated lactose with a spatula. The homogeneity of the mixtures was verified by the assay of ten 30 mg samples. The coefficient of variation of the sample content ranged between 1.1-3.0 for the mixtures studied. 27.4 mg+1.4 mg of the mixtures containing 400 .mu.g of salbutamol sulphate was filled into hard gelatin capsules (size 3).

Detailed Description Text (15):
A double blind randomised cross-over trial was carried out to compare the effects of a commercial formulation comprising salbutamol sulphate and a conventional lactose carrier with a composition according to this invention containing the same proportions of salbutamol sulphate and a modified lactose of this invention prepared in the manner described in Example 1. Eleven moderate to severe stable atopic asthmatic patients took part in the trial (FEV, <80% predicted; >15% reversibility. FEV is Forced Expiratory Volume in 1 second). The trial was carried out using conventional dry powder inhalers. The commercial formulation produced a mean increase in FEV, of 21.4%. The formulation according to this invention produced a mean increase in FEV, of 27.5%. The difference 6.1% was significant (paired t-test; $p<0.05$; confidence interval 0.64-11.52).

Detailed Description Text (17):
Lactose was recrystallised as in Example 1. Pentamidine isethionate was micronised at a pressure of 7.5 bar and a flow rate of 5 G/min and mixed with the lactose in the ratios 1:50, 1:20 1:10 and 1:5. Examination of the mixtures by scanning electron microscopy showed the formation of ordered mixing, the pentamidine forming layers of varying thickness on the substrate. After shaking the mix, samples were withdrawn and encapsulated. The uniformity of content indicated that the mixture possessed satisfactory stability.

Detailed Description Text (20):
Micronised disodium cromglycate (cromalyn) was mixed with equal parts in recrystallised lactose (prepared as in Example 1) by tumbling in a small mixer for 20 minutes. Examination by electron microscopy showed that the cromalyn was distributed as an even thick layer over the surfaces of the lactose. After shaking, samples were withdrawn and shown to be uniform in content. The stability of the mix thus permits handling in normal industrial processes.

Detailed Description Text (22):
Micronised beclomethasone dipropionate was mixed with recrystallised lactose (prepared as in Example 1) in the ratio of 1:67.5. Examination by electron microscopy showed that the components formed an ordered mixture with the steroid evenly distributed over the surface of the carrier. Subdivision showed that the distribution was uniform even after shaking. The stability of the mix thus permits handling in normal industrial processes.

Detailed Description Text (24):
Miconised disodium cromoglycate (dscg), with a mean particle size 2.8 .mu.m, was mixed with equal parts of the modified lactose (63-90 .mu.m) and tumbled in a small vessel for 15 minutes. 40 mg of the mix was distributed in capsultes which were then placed in a "rothaler" device. The respirable fraction was estimated using methods described in the British pharmacopoeia for quantifying the deposition of the emitted dose. Apparatus A (B.P. 1988 Appendix XVII C page A204) was used. The loaded rotahaler device was attached to the apparatus by means of an adaptor and air drawn through the assembly at 60 l/min. for each determination, five capsules were used and the experiment was repeated four times. The amount of drug retained in the device, in Stage 1 and in Stage 2 was measured by washing and spectrophotometric analysis. The entire experiment was repeated using a conventional crystallised lactose. The results, given in the table, are expressed as depositio in Stage 2(<6 .mu.m) as a percentage of the drug emerging from the device i.e. Stage 1+Stage 2.

Detailed Description Text (25):
The results show a significant increase in the respirable fraction when the modified lactose is used.

Detailed Description Text (27):
Terbutaline sulphate was micronised to give a mass median diameter of 1.3 mn (coulter counter) with 100% not more than 7 .mu.m). It was mixed with either conventional or modified lactose (prepared using the method of Example 1) in the ratio, 1 part drug to 65.5 parts carrier. Amounts of each powder corresponding to 500 .mu.g drug were placed in gelatin capsules (Size No. 3) and loaded in a "Rotahaler" device. A single capsule was discharge with a twin stage inpinger (as

described in Example 6 for DSCG) operated at 60 l/min. The amount of terbutaline retained in the device, on Stage 1 and on Stage 2 was measured by UV analysis. The experiment was repeated four times for each powder. The amount of drug deposited in Stage 2 and potentially respirable expressed as a % of the available dose (500 .mu.g) was

Detailed Description Text (28):
The coefficient of variable is given in parenthesis. Thus showing that the useful fraction of the dose is almost double when the modified lactose is used.

Detailed Description Paragraph Table (1):
TABLE I Percentage of drug deposited at various stages using regular lactose and recrystallised lactose. Regular lactose Recrystallised lactose At air flow rate of 601/min. Device 19.7 23.8 Preseparator 57.9 33.6 Stages 0-2 2.8 0.6 Stages 3-7 19.6 42.0 At air flow rate of 1501/min Device 15.2 24.4 Preseparator 76.8 51.5 Stages 0-2 2.6 2.6 Stages 3-7 5.4 22.0

Detailed Description Paragraph Table (2):
% DSCG Deposited in Stage 2
Modified lactose 25.0 24.9 24.7 26.5
Conventional lactose 18.8 18.6 18.6 18.7

Detailed Description Paragraph Table (3):
Conventional Lactose Modified Lactose
14.39 (0.15) 24.93 (0.12)

CLAIMS:

1. A crystalline particulate carrier suitable for use in dry powder inhaler compositions, wherein said carrier is a saccharide selected from the group consisting of a monosaccharide, a dissaccharide and a polysaccharide and having an average particle size of from 5.0 to 1000 microns and a rugosity as measured by air permeametry of less than 1.75.

5. A carrier according to claim 1, wherein the particles have a rugosity of not more than 1.5.

6. A carrier according to claim 2, which is a dissaccharide selected from the group consisting of sucrose and lactose.

7. A carrier according to claim 6, wherein the dissacharide is lactose.

L2: Entry 41 of 46 File: USPT Oct 19, 1993

DOCUMENT-IDENTIFIER: US 5254330 A
TITLE: Aerosol carriers

Abstract Text (1):
Pharmaceutical excipients useful in dry powder inhalents comprise particles having a rugosity (measured by air permeametry) of less than 1.75. The use of these carriers increases the amount of drug injested by the patient using a dry powder inhaler. The preferred excipients are crystalline sugars such as lactose which may conveniently be prepared by controlled crystallisation from an aqueous medium.

Brief Summary Text (3):
The present invention is directed to novel materials which are useful as carriers in dry powder inhaler compositions. We have discovered that the redispersion of drug particles from compositions comprising carriers is facilitated if the rugosity of the carrier particles is reduced. The rugosity values of the materials are those measured by air permeametry.Accordingly, from one aspect our invention provides a particulate carrier suitable for use in the preparation of pharmaceutical compositions having an average particle size of from 5.0 to 1000 microns and a rugosity of less than 1.75. The measurement of rugosity by air permeametry produces a result which reflects the nature of the external surface of the material under test whereas measurements by techniques such as nitrogen adsorption reflect the total surface area including areas which are not accessible to particulate solids. The rugosity of conventional excipients measured by air permeametry has been found to be at least 1.96 and generally greater than 2.0. The carrier may be any crystalline non toxic material which is acceptable for use in pharmaceutical compositions which does not destabilise the pharmaceutically active materials with which it is formulated and which can be produced in a form having a rugosity of less than 1.75. The preferred carriers are those which are known to be useful in dry powder inhaler compositions especially the mono-saccharides such as lactose, mannitol, arabinose, xylitol and dextrose and their monohydrates, dissacharides such as maltose or sucrose and polysaccharides such as starches, dextrins or dextrans.

Brief Summary Text (4):
Preferably the carrier comprises a particulate crystalline sugar such as glucose, fructose, mannitol, sucrose and most preferably lactose.

Brief Summary Text (6):
The particulate sugar crystals which constitute a preferred aspect, may be conveniently prepared by crystallisation from a solution which is preferably an aqueous solution. The conditions under which crystallisation occurs should be controlled so as to favour the production of crystals having the desired low degree of rugosity. In general conditions which allow the crystals to form slowly are preferred whilst those which result in rapid crystallisation are correspondingly less preferred. The utility of any particularly crystallisation process must be evaluated empirically and it is within the skill of the art to modify unsatisfactory procedures in order to produce the desired crystalline form of the novel excipients.

Brief Summary Text (9):
The size and morphology of the particulate material may be varied by controlling the conditions under which crystallisation and crystal growth occurs. In particular, the choice of the organic water immiscible solvent and the miscible solvent may exert a

considerable influence. Examples of water immiscible solvents which may usefully be employed include hexane, chloroform cyclohexane, and toluene. Examples of miscible solvents include acetone, alcohols and acetonitrile The requirement that the miscible solvent is at least partially miscible with the water immiscible solvent (and with water) means that the choice of immiscible and miscible solvents are interdependent. In the case of crystallisation of solutions of lactose, the preferred solvents are hexane (the immiscible solvent) and acetone (the miscible solvent). The quantities of solvent employed are preferably such as to provide an excess volume of immiscible solvent (typically at least 1.25 and more usually at least 1.5 times the volume of the saturated lactose solution being employed) and a relatively small quantity of the miscible solvent, say no more than 20% by volume being employed.

Brief Summary Text (11):
The form and size of the crystals may be determined by optical and/or scanning electron miscroscopy. The rugosity of the particles may be determined by air permeametry which relates the volumetric flow rate (Q) of air through a packed bed of powder compressed to a known porosity to the internal surface area So of the powder. The rugosity can then be expressed as the ratio So/Sd where Sd is the theoretical surface area (assuming the particles to be spherical). In practice the smoothness of the particles may be readily apparent under the scanning electron microscope and this may render the determination of their rugosity superfluous. Preferably the particles will have a rugosity of no more than 1.5 and most preferably no more than 1.3.

Detailed Description Text (4):
Lactose (lactochem Pharmaceuticals), in a size range of 63-90 .mu.m was obtained by sieving (Alpine air jet sieve).

Detailed Description Text (5):
Recrystallised lactose was obtained by crystallisation of the original lactose in a partially miscible mixture of water, hexane and acetone.

Detailed Description Text (6):
Lactose was dissolved in water (2 to 1) in a beaker at 80 C. The solution was cooled to room temperature, 75 ml of hexane (Reagent grade) was added to 50 ml of the saturated solution and agitated at 500 rpm with a paddle type agitator with four blades, acetone (10 ml) (Reagent grade) was then added. The mixture was stirred for 8-12 h, during which time lactose crystals formed. These were washed with acetone, absolute ethanol, 60% ethanol in water and absolute ethanol respectively and dried.

Detailed Description Text (7):
The particle size of the recrystallised lactose was determined with the optical microscope and was found to be in the range of 60-90 .mu.m. The examination of the carrier surface was by scanning electron microscopy. The rugosity of the lactose before and after crystallisation was determined by compressing a mass of powder equal to its density to a known porosity in the cell of a Fisher Sub-Sieve Sizer. The flow rate through the bed at a fixed pressure differential is transcribed by the instrument to an average particle diameter dm. The specific surface So was calculated from the equation ##EQU1## where p is the powder density. The rugosity before crystallisation was found to be 2.36 whilst the rugosity after recrystallisation was found to be 1.16.

Detailed Description Text (8):
Samples of drug -lactose blends were prepared in a ratio of 1:67.5 by mixing the micronised drug and the treated lactose with a spatula. The homogeneity of the mixtures was verified by the assay of ten 30 mg samples. The coefficient of variation of the sample content ranged between 1.1-3.0 for the mixtures studied. 27.4 mg+1.4 mg of the mixtures containing 400 .mu.g of salbutamol sulphate was filled into hard gelatin capsules (size 3).

Detailed Description Text (15):
A double blind randomised cross-over trial was carried out to compare the effects of a commercial formulation comprising salbutamol sulphate and a conventional lactose carrier with a composition according to this invention containing the same

proportions of salbutamol sulphate and a modified lactose of this invention prepared in the manner described in Example 1. Eleven moderate to severe stable atopic asthmatic patients took part in the trial (FEV,<80% predicted;>15% reversibility. FEV is Forced Expiratory Volume in 1 second). The trial was carried out using conventional dry powder inhalers. The commercial formulation produced a mean increase in FEV, of 21.4%. The formulation according to this invention produced a mean increase in FEV, of 27.5%. The difference 6.1% was significant (paired t-test; p<0.05; confidence interval 0.64-11.52).

Detailed Description Paragraph Table (1):

TABLE I Percentage of drug deposited at various stages using regular lactose and recrystallised lactose. Regular lactose Recrystallised lactose At air flow rate of 601/min. Device 19.7 23.8 Preseparator 57.9 33.6 Stages 0-2 2.8 0.6 Stages 3-7 19.6 42.0 At air flow rate of 1501/min Device 15.2 24.4 Preseparator 76.8 51.5 Stages 0-2 2.6 2.6 Stages 3-7 5.4 22.0

CLAIMS:

12. A composition according to claim 2, wherein the crystalline sugar is selected from a group consisting of glucose, fructose, mannitol, sucrose and lactose.

13. A composition according to claim 12, wherein the crystalline sugar is lactose.

L4: Entry 89 of 93 File: USPT Oct 11, 1994

DOCUMENT-IDENTIFIER: US 5354934 A
TITLE: Pulmonary administration of erythropoietin

Abstract Text (1):
Erythropoietin (EPO) can be delivered systemically in therapeutically or prophylactically effective amounts by pulmonary administration using a variety of pulmonary delivery devices, including nebulizers, metered dose inhalers and powder inhalers. Aerosol administration of EPO in accordance with this invention results in significant elevation of red blood cell levels. EPO can be administered in this manner to medically treat or prevent anemia, as well as to treat or prevent other maladies related to erythropoiesis.

Brief Summary Text (27):
In light of the foregoing, it is the object of this invention to provide a method for the pulmonary administration of a therapeutically effective amount of EPO to a mammal, such as a human. In one aspect of the invention, the methods described herein involve directing a therapeutically effective amount of EPO into the patient's oral cavity during inhalation. Such delivery may be accomplished through the use of a mechanical device. Examples of mechanical devices useful in accordance with the methods of the invention include metered dose inhalers, powder inhalers, and nebulizers, particularly jet nebulizers and ultrasonic nebulizers.

Detailed Description Text (9):
Devices capable of depositing aerosolized EPO formulations in the alveoli of a patient include nebulizers, metered dose inhalers, and powder inhalers. Other devices suitable for directing the pulmonary administration of EPO are also known in the art. All such devices require the use of formulations suitable for the dispensing of EPO in an aerosol. Such aerosols can be comprised of either solutions (both aqueous and non-aqueous) or solid particles. Nebulizers are useful in producing aerosols from solutions, while metered dose inhalers, dry powder inhalers, etc. are effective in generating small particle aerosols. Typically, each formulation is specific to the type of device employed and may involve the use of an appropriate propellant material, in addition to the usual diluents, adjuvants and/or carriers useful in EPO therapy. EPO formulations which can be utilized in the most common types of pulmonary dispensing devices to practice this invention are now described.

Detailed Description Text (11):
EPO formulations suitable for use with a nebulizer, either jet or ultrasonic, will typically comprise EPO dissolved in water at a concentration of, e.g., about 0.1 to 25 mg of EPO per mL of solution. The formulation may also include a buffer and a simple sugar (e.g., for protein stabilization and regulation of osmotic pressure), and/or human serum albumin ranging in concentration from 0.1 to 10 mg/ml. Examples of buffers which may be used are sodium acetate, citrate and glycine. Preferably, the buffer will have a composition and molarity suitable to adjust the solution to a pH in the range of 5 to 7. Generally, buffer molarities of from 2 mM to 50 mM are suitable for this purpose. Examples of sugars which can be utilized are lactose, maltose, mannitol, sorbitol, trehalose, and xylose, usually in amounts ranging from 1% to 10% by weight of the formulation.

Detailed Description Text (14):
Metered Dose Inhaler EPO Formulation

Detailed Description Text (15):
EPO formulations for use with a metereddose inhaler device will generally comprise a finely divided powder. This powder may be produced by lyophilizing and then milling a liquid EPO formulation and may also contain a stabilizer such as human serum albumin (HSA). Typically, more than 0.5% (w/w) HSA is added. Additionally, one or more sugars or sugar alcohols may be added to the preparation if necessary. Examples include lactose maltose, mannitol, sorbitol, sorbitose, trehalose, xylitol, and xylose. The amount added to the formulation can range from about 0.01 to 200% (w/w), preferably from approximately 1 to 50%, of the EPO present. Such formulations are then lyophilized and milled to the desired particle size.

Detailed Description Text (16):
The properly sized particles are then suspended in a propellant with the aid of a surfactant. The propellant may be any conventional material employed for this purpose, such as a chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol, and 1,1,1,2-tetrafluoroethane, or combinations thereof. Suitable surfactants include sorbitan trioleate and soya lecithin. Oleic acid may also be useful as a surfactant. This mixture is then loaded into the delivery device. An example of a commercially available metered dose inhaler suitable for use in the present invention is the Ventolin metered dose inhaler, manufactured by Glaxo Inc., Research Triangle Park, N.C.

Detailed Description Text (17):
Powder Inhaler EPO Formulation

Detailed Description Text (18):
Such EPO formulations will comprise a finely divided dry powder containing EPO and may also include a bulking agent, such as lactose, sorbitol, sucrose, or mannitol in amounts which facilitate dispersal of the powder from the device, e.g., 50% to 90% by weight of the formulation. The EPO should most advantageously be prepared in particulate form with an average particle size of less than about 10 .mu.m (or micrometers), most preferably 1 to 5 .mu.m, for most effective delivery to the distal lung.

Detailed Description Text (19):
An example of a powder inhaler suitable for use in accordance with the teachings herein is the Spinhaler powder inhaler, manufactured by Fisons Corp., Bedford, Mass.

Detailed Description Text (22):
As those skilled in the art will recognize, the operating conditions for delivery of a suitable inhalation dose will vary according to the type of mechanical device employed. For some aerosol delivery systems, such as nebulizers, the frequency of administration and operating period will be dictated chiefly by the amount of EPO per unit volume in the aerosol. In general, higher concentrations of protein in the nebulizer solution and, correspondingly, the aerosol will require shorter operating periods. Some devices, such as metered dose inhalers, may produce higher aerosol concentrations than others and thus will be operated for shorter periods to give the desired result.

Detailed Description Text (23):
Other devices, such as powder inhalers, are designed to be used until a given charge of active material is exhausted from the device. The charge loaded into the device will be formulated accordingly to contain the proper inhalation dose amount of EPO for delivery in a single administration.

Detailed Description Text (48):
While this invention has been specifically illustrated with regard to the use of aerosolized solutions and nebulizers, it is to be understood that any conventional means suitable for pulmonary delivery of a biological material may be employed to administer EPO in accordance with this invention. Indeed, there may be instances where a metered dose inhaler, or powder inhaler, or other device is preferable or best suits particular requirements. The foregoing description provides guidance as

to the use of some of those devices. The application of still others is within the abilities of the skilled practitioner. Thus, this invention should not be viewed as being limited to practice by application of only the particular embodiments described.

CLAIMS:

12. A method according to claim 11 wherein the mechanical device is selected from the group consisting of a nebulizer, a metered dose inhaler, and a powder inhaler.